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A Non-Hydrazine Monoamine Oxidase Inhibitor with Antihypertensive Properties. (26256)

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Previous studies in this laboratory have suggested that effective inhibition of monoamine oxidase (MAO) by various drugs in human hypertensives results in an orthostatic decrease in blood pressure(1-3). Agents of this type include iproniazid (Marsilid), trans - DL - 2-phenylcyclopropylamine (SKF-385, Parnate), β-phenylisopropylhydrazine (JB-516, Catron), phenylzine (Nardil), nialamide (Niamid), DL-serine-N^2-isopropylhydrazide (RO-4-1038)(4), and isocarboxazid (Marplan)(5). However, any final conclusion concerning a relationship between enzyme inhibition and blood pressure lowering has been tempered by the fact that, with the exception of SKF-385, all of these agents are hydrazine derivatives. Also, either because of low potency or occurrence of prohibitive toxicity, none have become valuable therapeutic agents in hypertension.

Thus, the discovery of the potent, non-hydrazine, MAO inhibitor, N-benzyl-N-methyl-2-propynylamine·HCl (MO-911), by Taylor *et al.*(6) was of special interest. This report presents initial results of administering this compound to human subjects. The findings give added support to the hypothesis that pronounced MAO inhibition produces an orthostatic decrease in blood pressure in hypertensive patients. Barring unforeseen toxicity, MO-911 appears to be a promising antihypertensive agent.

Materials and methods. The subjects were 4 females and 5 males, aged 26 to 51 years, with sustained hypertension uncomplicated except for renal insufficiency (pt. C.F.), polycystic kidneys (pt. C.M.) and unilateral pyelonephritis (pt. W.C.). Except for occasional one- to 3-day passes, the subjects were hospitalized throughout the periods of study. MO-911 was supplied as 25 mg scored tablets.* The only other medications were cardiac glycosides, barbiturates for sleep and salicylates. Salt intake was moderately restricted in one patient and calories in another.

Blood pressures (arm cuff technic) and pulse rates were measured 4 times daily in the supine position and also after 2 minutes of quiet standing. Control observations were made over a period of at least 6 days. Then, MO-911 was administered orally as a single dose before breakfast each day for periods of 14 to 34 days. Initial dosage was 75 to 125 mg/day with a downward revision when pronounced decline of blood pressure developed. With one exception, observations were extended for 8 to 17 days after cessation of therapy; during this time blood pressure levels approached or had returned to pre-treatment values.

Serial blood counts, urinalyses, tests of renal and hepatic function and periodic screening of visual acuity and color vision were performed to detect possible toxic effects. Degree of MAO inhibition was evaluated by daily assays of urinary tryptamine and tyramine(3).

Results. It was quickly established that MO-911 is an effective antihypertensive agent as well as a potent MAO inhibitor. Its long duration of action permitted achievement of sustained effects with use of single daily doses.

Effects on blood pressure and pulse rate. A pronounced fall in standing blood pressure

* Through the courtesy of Dr. R. K. Richards, Abbott Laboratories, N. Chicago, Ill.

TABLE I. Blood Pressure Response to MO-911.

Patient	Dose, mg/day	Avg blood pressures (mm Hg)* Control Supine	Control Standing	On drug Supine	On drug Standing	Change Supine	Change Standing
C.F.	37.5- 75	219/143	224/151	218/128	130/ 93	- 1/-15	-94/-58
W.C.T.	50 - 75	161/109	148/107	165/110	117/ 81	+ 4/+ 1	-31/-26
E.T.	75 -100	204/122	202/126	190/123	136/ 93	-14/+ 1	-66/-33
R.U.	50 -100	177/117	158/119	177/114	106/ 80	0/- 3	-52/-39
E.M.	50 - 75	203/124	181/123	174/102	118/ 84	-29/-22	-63/-39
C.M.	50 -125	164/117	156/121	192/120	138/108	+28/+ 3	-18/-13
M.K.	50 -125	213/146	188/149	205/135	129/106	- 8/-11	-59/-43
W.C.	50 - 75	220/137	211/149	222/134	148/108	+ 2/- 3	-63/-41
R.L.	25 - 75	154/113	148/120	169/120	124/ 98	+15/+ 7	-24/-22

* Each value is avg of 20 measurements in a period of 5 days prior to therapy (control) or at peak of drug effect (on drug).

occurred in each patient, average decreases ranging from 18 to 94 mm Hg in systolic and 13 to 58 mm Hg in diastolic pressure (Table I). In contrast, supine pressures were usually unchanged from control values. Time of onset for a pronounced orthostatic effect with doses of 75 to 125 mg/day varied from 7 to 20 days. After discontinuation of the drug, an orthostatic effect was usually discernible for 2 weeks or longer. Some of these relationships are illustrated by the findings in a typical case (pt. R.U.) (Fig. 1).

The patients did not develop tachycardia even in presence of profound decreases in standing blood pressure. Instead, alterations in pulse rate with posture were approximately the same as seen in the control state, with increases on standing of up to 18 beats per minute.

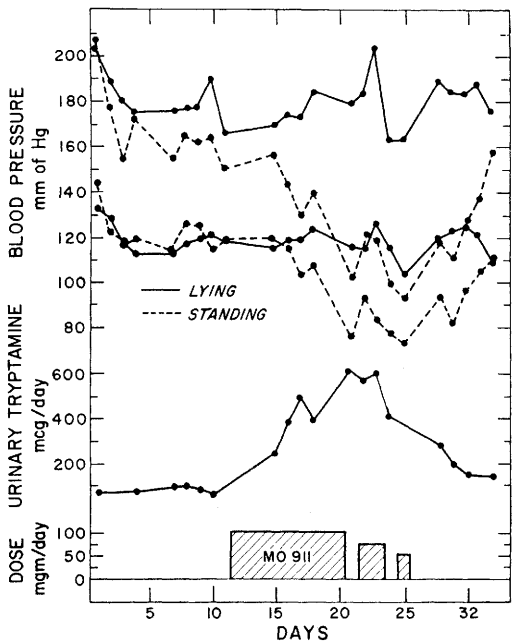

FIG. 1. Example of changes in blood pressure and urinary tryptamine with MO-911 (pt. R.U.).

MAO inhibition. Marked inhibition was shown by 4 to 11-fold rises in urinary tryptamine and similar changes in tyramine output, except in patient C.F. whose tryptamine rose from 65 to 220 μg/day; the lessened chemical response observed in this case is attributable to renal insufficiency (creatinine clearance of 50 ml/min). The tryptamine response shown in Fig. 1 indicates the usual magnitude of effect and general correlation with blood pressure changes.

Other effects. All patients maintained a sense of well being in spite of the marked alterations in blood pressure. Three showed heightened mood, 3 exhibited drowsiness early in treatment, one had slight morning dryness of the mouth, 2 had mild constipation, one had a disturbed sleep pattern, one had transient paresthesias, and one experienced an inability to ejaculate. Orthostatic dizziness occurred in some patients but could be obviated by a decrease in dose. There were no obvious changes in appetite. The aforementioned symptoms disappeared during the post-treatment period.

No abnormalities were noted in serial blood counts or in the results of tests of liver, renal and visual functions.

Discussion. This demonstration of the antihypertensive properties of MQ-911, whose

structure differs radically from that of previous MAO inhibitors, provides apparently conclusive evidence of a relationship between MAO inhibition and lowering of blood pressure. It is likely that the site of action is in the sympathetic nervous system since the blood pressure change is predominantly orthostatic and occurs in absence of reflex tachycardia or marked disturbance in parasympathetic functions. That specific sympathetic block may occur is indicated by the findings of Gertner(7) that several MAO inhibitors produced blockade of transmission through the perfused superior cervical ganglion of the cat, without interruption of responses to acetylcholine. Evidence of selective inhibition of sympathetic ganglia in the intact animal has been obtained by Goldberg and DaCosta(8). Assuming that the sympathetic block is due to MAO inhibition, mediation might be *via* increased tissue levels of amine(s). Norepinephrine must logically receive prime consideration and actually is known to have ganglion blocking properties (9). In support, Spector *et al.*(10) have recently reported that MAO inhibition results in increased levels of norepinephrine in the sympathetic ganglia of rabbits.

Much attention is now being given to therapeutic use of guanethidine (Ismelin) and bretylium tosylate (Darenthin)(11), agents which produce orthostatic hypotension *via* sympathetic blockade in absence of parasympathetic blockade. Our preliminary findings suggest that MO-911 compares favorably with these drugs and may also have desirable psychic properties. The drug is sufficiently potent to be used alone, although adjuvant agents could reasonably be expected to reduce dose requirements and might improve the responsiveness of some patients. The slow onset and long duration of its action are ideally suited to management of the ambulatory hypertensive. For initiation of treatment daily doses of 100 to 125 mg given under close observation are recommended. When the desired blood pressure effect has been established, the dose can be reduced to maintenance levels which will probably range from 37.5 to 75 mg/day. Alternatively one might begin treatment at 37.5 mg/day and increase the daily dose 12.5 mg every 2 weeks until optimal effect is obtained.

The effectiveness of MO-911 as an antihypertensive agent is considered established. From data in laboratory animals(6), it would appear to have a more favorable therapeutic index than has been available heretofore with MAO inhibitors. However, the question of chronic toxicity, particularly hepatic and neurologic reactions as encountered in some patients receiving hydrazine-containing inhibitors, can be resolved only by further clinical trial.

Summary. The compound, N-benzyl-N-methyl-2-propynylamine · HCl (MO-911), is shown to be a potent monoamine oxidase inhibitor in man, with hypotensive properties. Since its structure is different from that of previous inhibitors, the findings support the hypothesis that effective inhibition of monoamine oxidase results in orthostatic lowering of blood pressure, presumably by selective decrease of sympathetic nerve activity. Extensive clinical trial of the drug as an antihypertensive agent is warranted.

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